

Progress in Mathematical Biology Research

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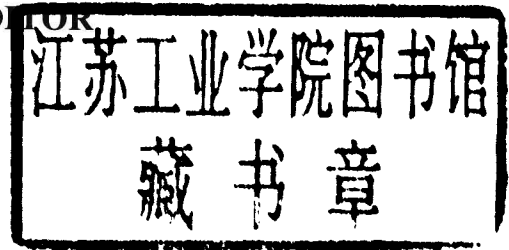
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James T. Kelly
Editor

**PROGRESS IN MATHEMATICAL
BIOLOGY RESEARCH**

JAMES T. KELLY

EDITOR



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PREFACE

Applying mathematics to biology has a long history, but only recently has there been an explosion of interest in the field. Some reasons for this include: the explosion of data-rich information sets, due to the genomics revolution, which are difficult to understand without the use of analytical tools, recent development of mathematical tools such as chaos theory to help understand complex, nonlinear mechanisms in biology, an increase in computing power which enables calculations and simulations to be performed that were not previously possible, and an increasing interest in *in silico* experimentation due to the complications involved in human and animal research. This new book presents the latest leading-edge research in the field.

In geometric knot theory, a central issue is to study the various geometric properties of knots when the knots have certain thickness. This setting makes a knot more like one that is tied with a uniform physical rope. These problems are mostly motivated by the recent applications of knot theory in fields such as biology and polymer chemistry. In Chapter 1, the authors will first give a brief review of the basic concepts and terminologies such as the thickness of a knot and the ropelength of a knot. They will then review the main results in this field. The topics will include results on the global minimum ropelength of knots, various lower and upper ropelength bounds of knots in terms of their crossing numbers, and lower and upper bounds on the total curvatures of thick knots. Some special families of knots or under different settings, such as lattice knots and smooth knots are also considered. While some proofs are omitted or only outlined due to the page limitation of the chapter, many important ideas, methods, and theorems are explained in depth. At the end of the chapter, a list of some open problems in this field is given.

In Chapter 2, the authors introduce new random dynamical systems generalizing neural networks with random sources. They study homeostasis of such system. Namely, following the viability theory, the authors suppose that there is a domain D in the phase space such that if the system state leaves D , the system will be destroyed.

Under some assumptions, the authors show that a generic system of such type is, in a sense, unstable under fluctuations. For a system with fixed parameters, the system state leaves D within the time T with a probability $P(T)$ such that $P(T) \rightarrow 0$ as $T \rightarrow \infty$. However, such systems can survive for large times, i.e., $P(T) > \delta > 0$ for all times, if the system parameters evolve in time.

Some arguments show that if fluctuations are, in a sense, strong, the parameters should be discrete. This allows to connect this evolution problem with theory of complexity and to show that the problem of survival may be very difficult, at least NP-hard.

The authors consider some morphogenesis problems for genetic networks. They show that these networks are capable to construct any spatio-temporal patterns. As an illustration, the segmentation problem in *Drosophila* is considered and the pattern stability problem is investigated.

Using some recent ideas for NP-complete problems, the authors formulate, as a hypothesis, "Freedom Principle": if a system has sufficiently many internal parameters to adjust, then the survival is possible, namely, there exists an effective heuristic algorithm of parameter evolution such that $P(T) > \delta > 0$ for all times T .

An exhaustive review of results involving topological sequence entropy is made in Chapter 3. Topological sequence entropy is an invariant by isomorphism which is an extension of the well-known notion of topological entropy. Topological entropy is one of the main tools to study chaotic dynamical systems. In this setting, topological sequence entropy can distinguish between chaotic and non-chaotic maps of zero topological entropy. The authors start by introducing metric sequence entropy (which is also an extension of metric entropy) in the setting of ergodic theory and discussing its properties. Similar properties will be satisfied also by topological sequence entropy although a variational principle which states the relationship between metric and topological entropies fails for sequence entropy. Finally, the authors see the relationship between topological sequence entropy and one of the most usual notions of chaos, Li-Yorke chaos, in the setting of one and two dimensional dynamics. They also give examples of computing explicitly topological sequence entropy for continuous interval maps and shift maps in symbolic spaces called substitution and Morse shifts.

A topological approach is used for the description and analysis of biological morphogenesis, and a topological interpretation of some morphogenetic events through the use of well known mathematical concepts and theorems is presented in Chapter 4.

The authors model the biological shape as a set of smooth, closed, oriented surfaces – membrane or epithelial layers. The spatial organization of membrane systems of eukaryotic cells may be represented topologically as a number of inner membrane surfaces embedded inside the outer cell membrane. During embryonic development and evolution process, the surface of an organism in most Metazoa undergoes spherical surgery (-ies), which change the topological genus of the surface. In some animal taxa topologically complicated fractal-like systems increases the genus of the surface; the body surface becomes topologically homeomorphic to a high-order torus.

Fractal-like biological structures are partially chaotic. To evaluate the relationship between order and chaos in the structure of epithelial branching fractal-like channels of the gastro-vascular system in the jellyfish *Aurelia aurita* and the larval tracheal gills of the mayflies *Siphonurus immanis* and *Parameletus chelififer* the authors compared these patterns in symmetrical parts of the organisms with deterministic fractal trees. The transition from order to chaos during morphogenesis of the dichotomously branching canals occurs as a cascade of bifurcations. The authors have shown that fractal dimension value may serve as a quantifier of neuronal spatial complexity correlating with cell morphology in several classes of encephalic neurons in the fishes *Pholidapus dybowskii* and *Oncorhynchus keta* and also with morphological changes of some spinal neurons during ontogenesis of *Oncorhynchus masou*.

Topological singularities of various fields on different levels of biological organization inevitably emerge and transform in biological morphogenesis. The authors studied cell morphogenetic fields and fractal self-organization in cell cultures *in vitro*. Two-dimensional cell direction fields with a defined set of topological singularities are shown in myogenic monolayer culture. The egg cleavage results in a pattern of cell contacts on the surface of the embryo as a discrete morphogenetic field.

Membrane and epithelial surfaces are boundary layers, interfaces between a living structure and its environment, ensuring metabolism. Fractal structures as well as toroid forms of Metazoa can be considered as functionally optimized biological design and attractors in biological morphogenesis. The authors can say that a certain set of topological rules, a “topological imperative”, constrains and directs biological morphogenesis.

As explained in Chapter 5, understanding the mechanisms behind the spatial patterns of species distributions is one of the major focuses in theoretical ecology. Spatial modelling techniques such as lattice models and cellular automata bring numerous spatial patterns in ecology. Taking spatial factors into account also helps to solve many puzzles in ecology, such as the paradoxes of diversity, polymorphism and altruism. To analyze the numerous spatial patterns, ecologists introduced the moment approximation from statistical physics. Spatial analysis of species distributions can also find its roots in the sampling statistics of ecology. Based on aggregation indicators (e.g. Lloyd’s indices and joint-count statistics), ecologists are able to distinguish the degree of non-randomness from spatially implicit and explicit perspectives, with over-dispersal and spatial autocorrelation as the synonyms of aggregation, respectively. Such sampling statistics also leads to the occupancy-abundance relationship with valuable applications in conservation. Although both spatial modelling and spatial analysis aim to achieve a profound understanding of species spatial patterns, they barely intersect. Through building the connections between sampling statistics and moment (pair) approximation, the authors unveil the relationship between the sampling density (mean abundance) and the colonization-extinction process. The intersection also solves the scaling pattern of species distribution by applying the pair approximation and the Bayesian rule into the joint-count statistics. By a scaling metapopulation model, the authors found that randomness is the bridge linking sampling statistics and spatial modelling, as well as the spatially implicit and explicit patterns. This intersection also sheds light on the occupancy-abundance relationship and the connection between spatial patterns and species life-history traits. In this exercise, the authors emphasize the importance and potential of bringing these two schools of knowledge together in understanding ecological complexity. Ten merging questions that require this intersection have been presented to expound on possible applications to the species distribution and the community structure in the near future.

Chapter 6 reviews recent mathematical models of the epizootic of Hantavirus in mice populations. The models are mainly based on field observations of *Peromyscus maniculatus* populations in New Mexico, which hosts Sin Nombre virus. The sporadic disappearance of the infection during times of adverse conditions is explained as a phase transition controlled by the environment. Refinements of the model allow to include the effect of non-host competitors, as well as to assess the validity of the diffusion transport. A stochastic model, based on individual interactions, is also analyzed. The authors compare its macroscopic limit with the mean field model, and discuss some phenomena inherent to stochastic systems: the role of fluctuations, extinctions and stabilization of oscillations.

In Chapter 7, the authors present an approach that can be useful to molecular biologists interested in studying genetic networks. The proposed methods can be applied to choose experiments to investigate a particular biological function. Considering a genetic network and some steady states obtained from experimental data for that system, they designed two reverse engineering procedures allowing us to determine two types of subnetworks of interest: necessary network and minimum networks. A necessary network is the subnetwork where all the interactions are necessary in order to conserve the observed steady states. Minimum networks are the subnetworks where the steady states are conserved and where none of the interactions can be removed from them. The authors considered, in this article, a genetic network involved in the segmentation of the fly embryo. Generalized Logical Analysis and constraint programming have been used in this study. In addition, considering the same example, the authors show that they could select any model among myriads of valid ones in order to simulate mutations. Indeed, experimental results indicate that the designed tests lead to identical results for any chosen model.

There have been an approach to fractal geometry using the notion of approximate sequences. Approximate sequences are inverse systems with some extra information that is useful in representing the properties of topological spaces. In the inverse system approach to fractal geometry, this information is used to represent fractal notions such as box-counting dimension, Hausdorff dimension, and Lipschitz functions. This approach gives a systematic and categorical framework for fractal notions. However, most of the papers which have appeared so far are based on approximate sequences which are not commutative. Approximate sequences which are not commutative make the setting very technical and restrict the audience, although it is general and more applicable. In Chapter 8 is constructed the inverse system approach to fractal geometry using a simplified version of approximate sequences, that is, commutative approximate sequences, so that scientists without the knowledge of approximate sequences can easily study this approach.

Sexual dimorphism, as seen from the standpoint of biologists, is conceptually clear, its existence offers no doubts, and its importance as a component of the form variation in biological populations is well known. When sexual dimorphism has been mathematically formulated, however, there have arisen some misinterpretations regarding its definition, the wide variety of measures, or indices, by which it is assessed being the main reason. Chapter 9 surveys most of the different sexual dimorphism indices that have been proposed and with this aim the following three assumptions have been made. The first one is that a random variable and its distribution function - the population of measures of the biological trait under study as well as the rule governing the probabilistic behavior of such measures - are involved. The second one is that, in comparing the female and male populations, to be concerned with only partial features of such populations, as for example their mean parameters, does not seem the most appropriate; rather, on the contrary, the population as a whole should be considered, which means that distribution functions are the objects to be analyzed. Finally, the third assumption is related with the researcher inaccessibility to all observations of a population; this, as is widely known, is the same as to say that, being random samples implicated, it seems advisable to take some inferential procedure into account. In view of the indices of sexual dimorphism here examined, it is concluded that most of them account for only partial characteristics of the populations involved and they fail to incorporate an inferential support.

In Chapter 10, using a discrete deterministic model, the ergodicity of an age-structured population with an additional structure is investigated, and its autonomous first integral computed. The processes under consideration are Markovian and one of their basic attributes is that they are either conservative or dissipative (systems). Next, this population dynamics problem with an additional structure is transformed into an abstract Cauchy problem which is explicitly solved using functional analytic method. Instead of using the familiar theory of resolvent, the condition of well-posedness is replaced by its equivalent form in order to prove the existence of a unique weak solution. An *a priori* estimate of the solution is also given as well as the perturbation about the equilibrium point and by a bounded linear operator.

The knowledge of the nerve impulse in medicine is of particular relevance to the improvement of medical diagnostic and therapeutic methods. The electrochemical behaviour of the axon membrane plays an important and key role in the resulting nerve impulse, which can be related to the movement of ions between the extra and intracellular regions due to the active and the passive transports. In Chapter 11 the authors present a new contribution for the understanding of the diffusion process in a biological membrane of an axon. The problem is formulated for the sodium current from the electromagnetic theory. Indeed from the Maxwell equations the authors state a mathematical model considering the Fick-Ohm law for the total electrical current density. An analytical solution is proposed under different physiological parameters.

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Chapter 1

GEOMETRIC PROPERTIES AND PROBLEMS OF THICK KNOTS

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Abstract

In geometric knot theory, a central issue is to study the various geometric properties of knots when the knots have certain thickness. This setting makes a knot more like one that is tied with a uniform physical rope. These problems are mostly motivated by the recent applications of knot theory in fields such as biology and polymer chemistry. In this chapter, we will first give a brief review of the basic concepts and terminologies such as the thickness of a knot and the ropelength of a knot. We will then review the main results in this field. The topics will include results on the global minimum ropelength of knots, various lower and upper ropelength bounds of knots in terms of their crossing numbers, and lower and upper bounds on the total curvatures of thick knots. Some special families of knots or under different settings, such as lattice knots and smooth knots are also considered. While some proofs are omitted or only outlined due to the page limitation of the chapter, many important ideas, methods, and theorems are explained in depth. At the end of the chapter, a list of some open problems in this field is given.

1. Introduction

In this chapter, we will discuss the geometric properties of knots when they are considered as physical subjects, that is, when the knots are tied with ropes which have thickness and

volume. This is in sharp contrast with the traditional mathematical treatment of knots which views knots as volumeless simple closed curves in the 3-dimensional space \mathbb{R}^3 . It is well known that knots play an important role in studying the behavior of various enzymes known as topoisomerases, see for example [15, 39, 40, 62, 66, 67]. Since the (effective) diameter of DNA can be measured, it is possible to model it as a rope with certain physical properties, see for example [58, 60]. It is also important to recognize the volume occupying nature and the geometric shapes of physical knots [42]. An essential issue here is to relate the length of a rope (with certain thickness) to those knots that can be tied with this rope. Such information plays an important role in studying the effect of topological entanglement in subjects such as circular DNA and long chain polymers, where knots occur and cannot be treated as volumeless curves.

To model a physical knot that is smooth (as that of a uniform rope), the concept of *thickness* of a knot is introduced. The *thickness* of a smooth knot can be thought of, intuitively, as the radius of the largest embedded normal tube around the knot, although slight variations of the definition do exist. See for example Cantarella, Kusner and Sullivan [12], Diao, Ernst and Janse van Rensburg [27], and Litherland, Simon, Durumeric and Rawdon [47]. A *thick knot* is a smooth knot with a positive thickness and the *ropelength* of a thick knot K is the quotient of its arclength over its thickness and is denoted by $L_r(K)$. This quotient ensures that the ropelength is independent of the actual thickness of the tube. The ropelength minimizing configuration of a given knot type is called an *ideal knot* or a *tight knot*. It is proven by Cantarella et al [12] that the ropelength minimizer of any given knot type exists. However, it is an extremely hard problem to find the exact ropelength of a nontrivial knot. In fact, the exact ropelength is not known for any nontrivial one component knot. Consequently, most works concerning (one component) ideal knots are either numerical studies on small knots or are devoted to establishing theoretical lower or upper ropelength bounds, see for example the collection of articles in the book [61] edited by Stasiak, Katritch, and Kauffman and [17, 22, 23, 24, 28, 29, 33, 35, 53, 55, 59].

In this chapter, we will first discuss the concept of thickness in more details and outline a few well known and important results about it. We will then discuss the lattice knots and the relationship between smooth thick knots and lattices knots in terms of their lengths (as lattice knots are easier to treat sometimes). We will then give a detailed account of the results on the ropelength of thick knots ($L_r(\mathcal{K})$) with a focus on lower and upper bounds. This includes the global ropelength lower bound of all nontrivial knots, the general ropelength lower bound of a nontrivial knot in terms of its crossing number, the general ropelength upper bound of a nontrivial knot in terms of its crossing number, and the ropelength bounds for some special classes of knots. We will also include results on the upper and lower bounds of total curvature of nontrivial thick knots in terms of their crossing numbers, as well as the bounds on linking numbers in terms of the length of a thick link with two components. We conclude this chapter with a list of open questions.

2. Some Basic Facts of Knot Theory

Let K be a smooth knot (or link), that is, a smooth embedding of the unit circle (or circles) into \mathbf{R}^3 . A continuous map $H : I \times \mathbf{R}^3 \longrightarrow I \times \mathbf{R}^3$ (where $I = [0, 1]$) is called an *ambient isotopy* if, for each fixed $s \in [0, 1]$, $H(s, x)$ is a homeomorphism from \mathbf{R}^3 to \mathbf{R}^3 . Two knots (or links) K and K' are said to be of the same *knot type* \mathcal{K} if there exists an ambient isotopy $H : I \times \mathbf{R}^3 \longrightarrow I \times \mathbf{R}^3$ such that $H(0, x)$ is the identity map on \mathbf{R}^3 and $H(1, x)$ maps K to K' . It is easy to see that the knot type defines an equivalence relation among all smooth or piecewise smooth knots. We say that K is a *trivial knot* if K is of the same knot type as that of a unit circle in \mathbf{R}^3 . We say that K is a *nontrivial knot* if it is not a trivial knot.

The projection of K into a plane Π is a closed curve (or collection of closed curves if K is a link) in Π that may contain self-intersecting points, such a projection is denoted by $P_{\vec{v}}(K)$ where \vec{v} is a unit vector normal to Π . A self-intersecting point is also called a *crossing* of $P_{\vec{v}}(K)$. The *multiplicity* of a crossing in the projection is the number of strands that pass through that point. We say that $P_{\vec{v}}(K)$ is a *regular projection* or *diagram* if there are only finitely many crossings in $P_{\vec{v}}(K)$ and all crossings are of multiplicity 2. Furthermore, at each crossing in a regular knot projection, the strand that goes over and the strand that goes under are also marked, see Figure 1. With this additional information from over-strand and under-strand, one can easily reconstruct a knot K' such that K' and K have the same knot type and have the same knot projection. It is a well-known result for any (piece-wise smooth) knot K , its projection is a regular projection for almost all projection directions.

A common measure for the complexity of a knot or link type \mathcal{K} is its *crossing number*, which is the minimum number of crossings of $P_{\vec{v}}(K)$, taken over all vectors \vec{v} and all knots K of knot type \mathcal{K} where $P_{\vec{v}}(K)$ is a regular projection. The crossing number of \mathcal{K} is denoted by $Cr(\mathcal{K})$ or often by $Cr(K)$. Of course, by this definition, if K and K' are of the same knot type \mathcal{K} , then $Cr(K) = Cr(K')$. We say that $P_{\vec{v}}(K)$ is a *minimal diagram* of K if it is a regular projection with $Cr(\mathcal{K})$ crossings.

A knot K is called a *composite knot* if (1) there exists a topological 2-sphere S^2 such that K intersects S^2 in exactly two points and (2) two nontrivial knots are formed when the two parts of K that are inside and outside S^2 are joined by a simple curve on S^2 between the points of $K \cap S^2$. We say that K is a *prime knot* if it is not a composite knot. A composite knot K can be easily constructed from two nontrivial knots K_1 and K_2 as shown in Figure 1 by cutting the dashed arcs from K_1 and K_2 and then adding the two arcs as shown in Figure 1. We say that K is a *connected sum* of K_1 and K_2 in this case and also denote K by $K_1 \# K_2$. One can similarly define the connected sum of more than two knot components.

The following theorems are classical results in knot theory [7].

Theorem 2.1. *Any nontrivial knot K can be decomposed as the connected sum of some prime knots. That is, for any nontrivial knot K , there exist prime knots K_1, K_2, \dots, K_j*

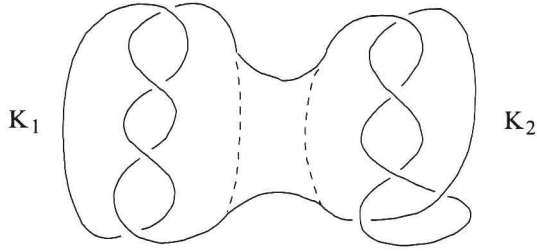


Figure 1. A regular projection of a composite knot: the left component has four crossings and the right component has five crossings.

($j \geq 1$) such that $K = K_1 \# K_2 \# \dots \# K_j$.

Theorem 2.2. For any knots K_1 and K_2 , we have $Cr(K_1 \# K_2) \leq Cr(K_1) + Cr(K_2)$. If K_1 and K_2 are alternating knots, then we have $Cr(K_1 \# K_2) = Cr(K_1) + Cr(K_2)$.

It is still an open problem whether $Cr(K_1 \# K_2) = Cr(K_1) + Cr(K_2)$ is true for any two knots K_1 and K_2 . The concept of prime knots can be applied to links as well. However, when there is more than one component present in either K_1 or K_2 , the connected sum $K_1 \# K_2$ is not well-defined unless we specify to which component the connection is to be made. As long as we understand that there is a choice of components involved in $K_1 \# K_2$ (even though it is not spelled out explicitly), the above theorems still hold in the case of links.

3. Thicknesses of Knots

There are different ways to define the thickness of a knot [12, 27, 44, 47, 53]. The conceptually easiest definition of thickness is the so called *disk thickness* introduced in [47] and described as follows. Let K be a C^2 knot. A number $r > 0$ is said to be *nice* if for any distinct points x, y on K , we have $D(x, r) \cap D(y, r) = \emptyset$, where $D(x, r)$ and $D(y, r)$ are the discs of radius r centered at x and y which are normal to K . The *disk thickness* of K is defined to be $t_D(K) = \sup\{r : r \text{ is nice}\}$.

Let $\alpha(s)$ be an arclength parameterized equation of K . A pair of points $(x_1, x_2) = (\alpha(s_1), \alpha(s_2)) \in K$ are called *double critical points* if $(x_2 - x_1) \cdot \alpha'(s_1) = (x_2 - x_1) \cdot \alpha'(s_2) = 0$. It is obvious that for any smooth K , there exist at least one pair of double critical points. We may thus define the set of all such double critical point pairs by $C(K)$ following the notation in the article of Litherland et al [47], which also contains following theorem.

Theorem 3.1. [47] For any C^2 knot K , its thickness $t_D(K)$ is given by

$$t_D(K) = \min\{1/\kappa, d(K)\},$$

where κ is the maximum curvature of the curve K and

$$d(K) = \frac{1}{2} \min_{x_1, x_2 \in C(K)} \|x_2 - x_1\|$$

is the minimum separation between any two double critical points in K .

The disk thickness definition can be extended to more general curves including C^1 and $C^{1,1}$ curves. We will introduce three such notions.

The simplest approach to generalize the disk thickness $t_D(K)$ allows the intersections of disks normal to K [27]. In a sense these are ways to model knots tied with non-uniform ropes. First, for any two points x and y on a smooth knot K , we will let $s(x, y)$ be the length of the shorter arc on K between the points x and y .

Definition 3.2. [27] Let K be a C^1 smooth knot. Fix an $\epsilon \in [0, 2\pi/3)$. Then c is an ϵ -nice number if $D_x(c) \cap D_y(c) = \emptyset$ for all $x, y \in K$ such that $s(x, y) \geq \epsilon c$. The T_ϵ -thickness of K is defined as

$$T_\epsilon(K) = \sup\{t : t \text{ is } \epsilon\text{-nice}\}.$$

It is obvious that $T_0 = t_D(K)$ and that $T_\epsilon(K)$ is a non-decreasing function of ϵ for each fixed K . The reason for the condition $\epsilon < 2\pi/3$ can be seen in the following example. Consider the unit circle with three points on it separated by arclength $2\pi/3$. Now push the three points slightly inward so that the resulting curve remains smooth and the normal planes at the three points all contain the y -axis. For most values of ϵ the thickness of the new curve is defined by the minimal normal disks around these three points. By making the deformation of the circle very small, we obtain a curve whose thickness is as close to 1 as we choose. But for some $\epsilon > 2\pi/3$, these three points will not be used in the calculation of the thickness. As a result, we will get a thickness of one. Thus we will be able to find a $c > 0$ that is close enough to 1 so that the c -neighborhood of the curve is no longer a solid torus. Thus T_ϵ is no longer a valid thickness for K , see Theorem 3.4.

The second definition of another thickness is similar to $T_\epsilon(K)$ in the sense that is parameterized by ϵ as well but it is different because it is defined in terms of a more explicit formula.

Definition 3.3. [27] Let K be a C^1 smooth knot with an arclength parameterized equation $\alpha(s)$. Fix an $\epsilon \in [0, 2\pi/3)$. Then the t_ϵ -thickness of K is defined as

$$t_\epsilon(K) = \inf_{x, y \in K} \left\{ \frac{\|x - y\|}{2 \sin \theta(x, y)} : \frac{2 \sin \theta(x, y) \cdot s(x, y)}{\|x - y\|} \geq \epsilon \right\},$$

where $\theta(x, y)$ is the smaller angle between T_x (the tangent vector of K at x) and $y - x$.

The condition $\frac{2 \sin \theta(x, y) \cdot s(x, y)}{\|x - y\|} \geq \epsilon$ is called the *controlling condition* and the function $\frac{2 \sin \theta(x, y) \cdot s(x, y)}{\|x - y\|}$ is called the *controlling function*. The set of all points $(x, y) \in K \times K$ satisfying the controlling condition is denoted by M_ϵ .

It is easy to see that $t_\epsilon(K)$ is a non-decreasing function of ϵ for each fixed K since we have $M_{\epsilon_1} \subseteq M_{\epsilon_2}$ whenever $\epsilon_1 > \epsilon_2$.

However, it is much less obvious that $t_0(K)$ exists and defines a meaningful thickness and that it equals $t_D(K)$ (when K is a C^2 curve). The fact that $t_\epsilon(K) > 0$ is defined for any $\epsilon > 0$ follows from the following reasoning: the limit of the controlling function $\frac{2 \sin \theta(x,y) \cdot s(x,y)}{\|x-y\|}$ is 0 if $x = y$. Thus the controlling function can be thought of as a continuous function over the compact set $K \times K$. Since M_ϵ is a closed subset of $K \times K$, it is also compact. M_ϵ is not empty as long as $\epsilon \leq 2\pi/3$ (this is actually not so obvious, see [27] for a full discussion). In addition, $\sin \theta(x, y)$ is bounded away from 0 on M_ϵ . Hence, $\frac{\|x-y\|}{2 \sin \theta(x,y)}$ is a continuous function on M_ϵ . It follows that there exists $(x_0, y_0) \in M_\epsilon$ such that

$$t_\epsilon(K) = \inf_{(x,y) \in M_\epsilon} \left\{ \frac{\|x-y\|}{2 \sin \theta(x,y)} \right\} = \frac{\|x_0 - y_0\|}{2 \sin \theta(x_0, y_0)}.$$

Since $x_0 \neq y_0$, thus $\|x_0 - y_0\| > 0$ and so $t_\epsilon(K) > 0$.

In the case that $\epsilon = 0$ and K is a C^2 curve, $M_0 = K \times K$. In this case, $\sin \theta(x, y)$ is not bounded away from 0. However one can show that

$$\lim_{y \rightarrow x} \frac{\|x-y\|}{2 \sin \theta(x,y)} = \frac{1}{\kappa(x)},$$

where $\kappa(x)$ is the curvature of K at x . Furthermore, this limit converges uniformly on K . Thus, $\frac{\|x-y\|}{2 \sin \theta(x,y)}$ can be extended to a continuous function on $K \times K$. It then becomes clear that $p = \max\left\{ \frac{\|x-y\|}{2 \sin \theta(x,y)} \right\} > 0$ exists and that $t_0(K) = t_D(K)$. See [27] for a full discussion.

The following theorem guarantees that t_ϵ and T_ϵ are valid thicknesses under the given condition $\epsilon \leq 2\pi/3$.

Theorem 3.4. [27] $T_\epsilon(K)$ defines a thickness of K , i.e., $K(c)$ is a solid torus which is homotopic to K via a strong deformation retract for every $c < T_\epsilon(K)$, where $K(c)$ is the c -neighborhood of K , namely the set of all points in \mathbb{R}^3 that are within a distance c from K . Similarly, $t_\epsilon(K)$ also defines a thickness of K .

First one shows that $t_\epsilon(K) \leq T_\epsilon(K)$ for each ϵ . Thus it suffices to show Theorem 3.4 for $T_\epsilon(K)$. The proof that $T_\epsilon(K)$ defines a thickness for K is not trivial. The following lemmas give an outline leading to the proof of this fact.

Lemma 3.5. [27] For each C^1 smooth knot K , there exists $c_0 > 0$ such that $K(c)$ is a solid torus (with K as its center curve) which is homotopic to K via strong deformation retract for any c such that $0 < c \leq c_0$.

Proof. The goal of the proof is to define a product structure $K \times D(x)$ on $K(c)$, where $D(x)$ is a planar disk containing x in its interior such that $D(x) \cap K = x$. This product structure is then used to define a strong deformation retract from $K(c)$ to K . The entire proof of this fact is rather technical and tedious. See [27] for the details. \square